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Thrombogenicity of Mechanical Circulatory Support Devices: Experience and Challenges from Design to Clinical Use

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Heart Failure

- Cardiovascular disease is the leading cause of mortality globally (Lloyd-Jones et al., 2010).
- Among various forms of cardiovascular disease, heart failure (HF) affects **5.8 million** patients in the US (WHO. Fact Sheet No. 317)
- The fatality rate for HF is high, with **1 in 5 people** dying within 1 year and fewer than **60 %** surviving 5 years
- The estimated direct and indirect cost of HF in the United States for 2010 is **$39.2 billion**

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Treatments for Heart Failure: Lifestyle and Medicine

Lifestyle Changes

Medications:

- Angiotensin-converting enzyme (ACE) inhibitors.
- Angiotensin II receptor blockers
- Digoxin (Lanoxin)
- Diuretics
- Aldosterone antagonists

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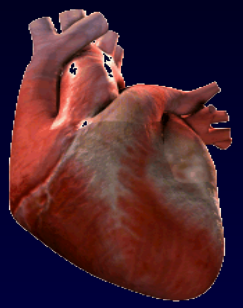
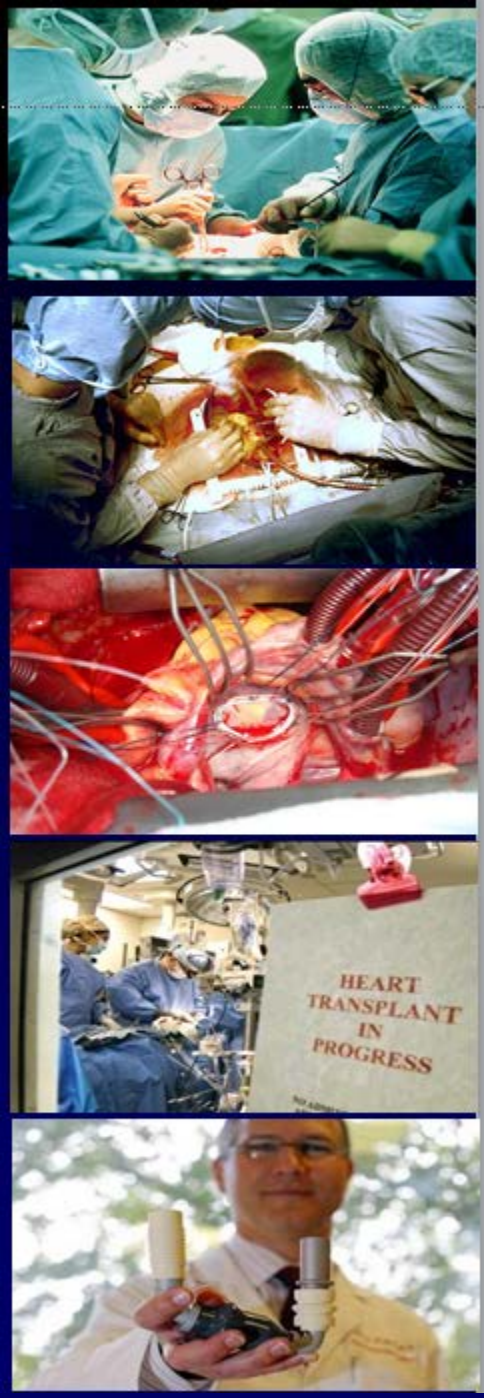
Treatments for Heart Failure



Surgery and Medical Devices

- Coronary bypass surgery
- Heart valve repair or replacement
- Implantable cardioverter-defibrillators (ICDs)
- Cardiac resynchronization therapy/ biventricular cardiac pacemaker
- Heart transplant
- Heart pumps (mechanical circulatory support devices)



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Circulatory Support Device

A circulatory support device or ventricular (VAD) is a mechanical pump that's used to support heart function and blood flow in people who have weakened hearts. The device takes blood from a lower chamber of the heart and helps pump it to the body and vital organs, just as a healthy heart would.

A VAD can support heart:

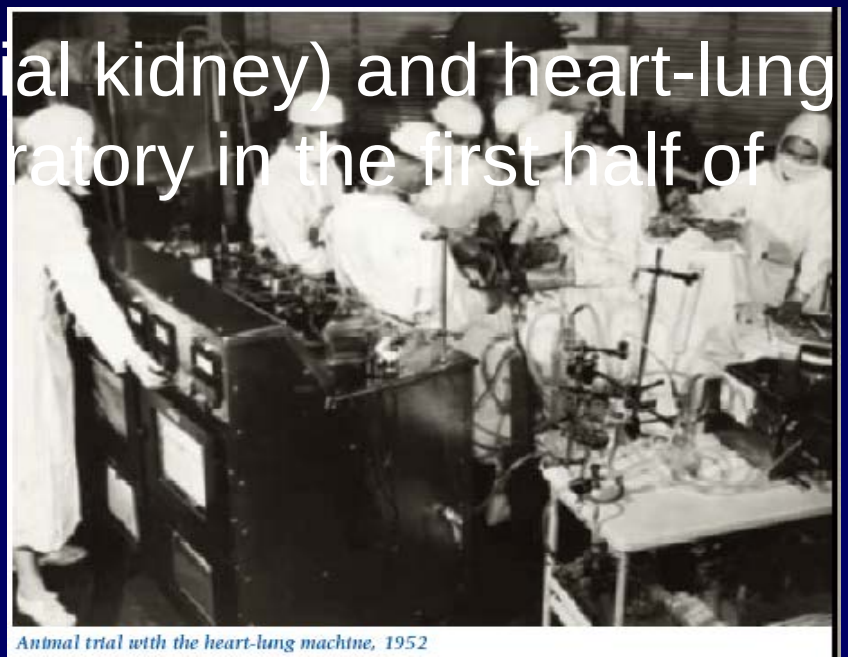
- During or after surgery, until heart recovers
- While waiting for a heart transplant
- If not eligible for a heart transplant, a VAD can be a long-term solution (destination therapy).

John and Mary Gibbons

1953

Birth of Cardiopulmonary Bypass

- The history of cardiovascular medical devices can be traced back to the 19th century. In 1885. M. von Frey and M. Gruber (Leipzig) built and used the first artificial heart-lung apparatus for organ perfusion studies.
- Various hemodialyzers (artificial kidney) and heart-lung apparatus were tested in laboratory in the first half of the 20th century.



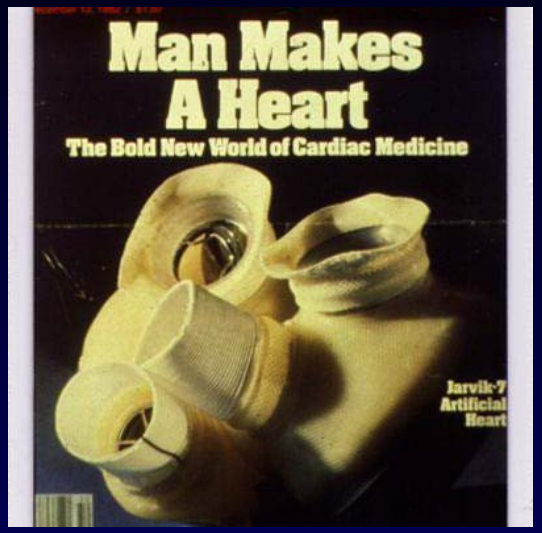
Animal trial with the heart-lung machine, 1952

Artificial Hearts and Ventricular Assist Devices

1956

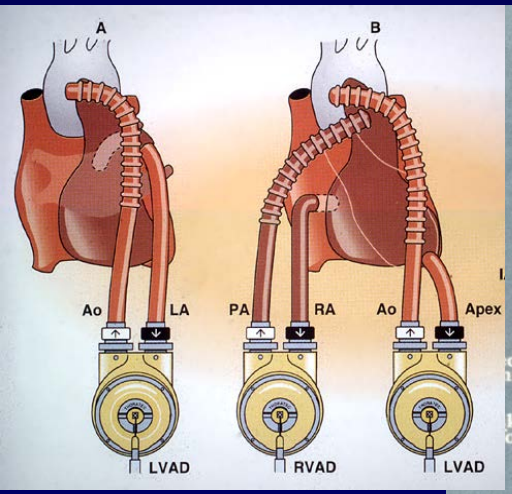
1966

1982

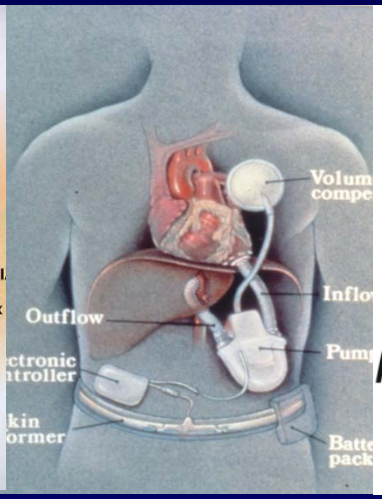


2001

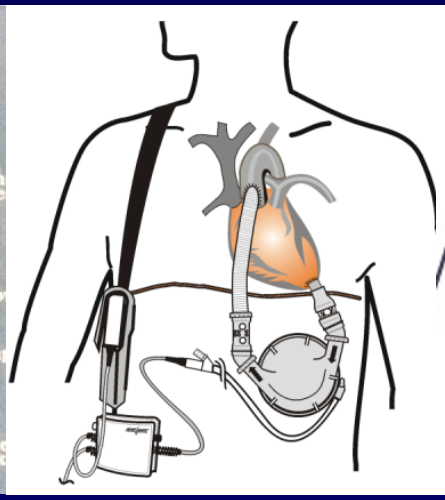
1995



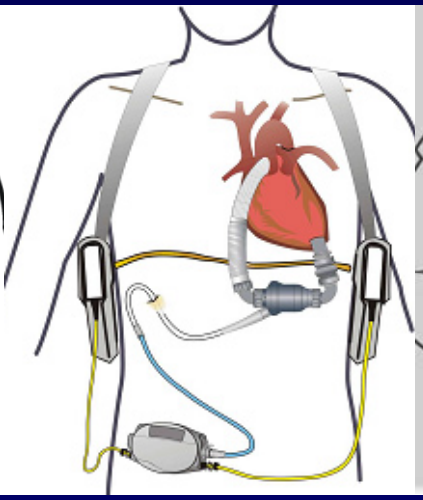
1998



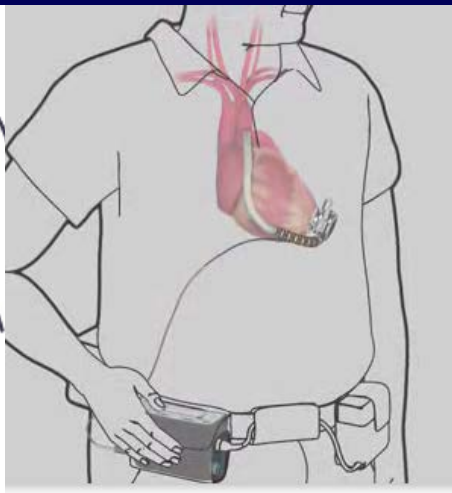
2001



2008



2012



INTERMACS Registry
Interagency Registry for Mechanically Assisted Circulatory Support

Table 2 Current approved and investigational surgically implanted devices for circulatory support

Device	Mechanism	Type	United States (FDA)	Europe (CE mark)	Anticoagulation
Thoratec PVAD	Pneumatic, pulsatile	Paracorporeal	Approved BTT	Approved BTT	Required
Thoratec IVAD	Pneumatic, pulsatile	Intracorporeal	Approved BTT	Approved BTT	Required
Thoratec HeartMate XVE	Electric, pulsatile	Intracorporeal	Approved BTT, DT	Approved BTT, DT	Not required
BerlinHeart EXCOR	Pneumatic, pulsatile	Paracorporeal	Investigational	Approved BTT	Required
Thoratec HeartMate II	Electric, axial continuous flow	Intracorporeal	Approved BTT, DT	Approved BTT, DT	Required
HeartWare LVAS	Electric, centrifugal continuous flow	Intracorporeal	Approved BTT	Approved BTT, DT	Required
Levitronix/Thoratec Centrimag	Electric, centrifugal continuous flow	Extracorporeal	Approved BTD (6 h), temporary RVAD (30 days), ongoing investigation	Approved BTD, BTT	Required
Jarvik FlowMaker	Electric, axial continuous flow	Intracorporeal	Investigational	Approved BTT, DT	Required
Micromed DeBakey HeartAssist 5	Electric, axial continuous flow	Intracorporeal	Approved Pediatric BTT, ongoing Investigation	Approved BTT, DT	Required
Terumo DuraHeart	Electric, centrifugal continuous flow	Intracorporeal	Investigational	Approved BTT, DT	Required
BerlinHeart INCOR	Electric, axial continuous flow	Intracorporeal	Investigational	Approved BTT, DT	Required
SynCardia TAH	Pneumatic, pulsatile	Intracorporeal	Approved BTT	Approved BTT	Required
Abiomed Abiocor TAH	Electrohydraulic, pulsatile	Intracorporeal	Humanitarian IDE DT	Investigational	Required

BTT bridge to transplant, *DT* destination therapy, *IDE* investigational device exemption, *RVAD* right ventricular assist device

J Heart Lung Transplant 2012;31:117–26

REMATCH Trial

Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure

Optimal Medical Therapy Vs. LV Assist Device (HeartMate I)

Vs.

N Engl J Med 2001;345:1435-43

Adverse Event Rates

Table 5 Implants: June 2006–June 2012[a]

	Pulsatile (n = 504)		Continuous (n = 5,358)		Pulsatile/Continuous	
Adverse event	Events	Rate	Events	Rate	Ratio	p-value
Device malfunction	119	3.26	660	1.60	2.04	<0.0001
Bleeding	630	17.28	3895	9.45	1.83	<0.0001
Cardiac/vascular						
Right heart failure	90	2.47	737	1.79	1.38	0.001
Myocardial infarction	2	0.05	30	0.07	0.75	0.47
Cardiac arrhythmia	254	6.96	1919	4.66	1.50	<0.0001
Pericardial drainage	64	1.75	251	0.61	2.88	<0.0001
Hypertension[b]	118	3.24	351	0.85	3.80	<0.0001
Arterial non-CNS thrombosis	14	0.38	74	0.18	2.14	0.001
Venous thrombotic event	59	1.62	289	0.70	2.31	<0.0001
Hemolysis	23	0.63	299	0.73	0.87	0.60
Infection	832	22.81	3302	8.01	2.85	<0.0001
Neurological dysfunction	139	3.84	764	1.83	2.08	<0.0001
Renal dysfunction	108	2.96	582	1.41	2.10	<0.0001
Hepatic dysfunction	48	1.32	247	0.60	2.20	<0.0001
Respiratory failure	206	5.65	1038	2.52	2.24	<0.0001
Wound dehiscence	18	0.49	76	0.18	2.75	<0.0001
Psychiatric episode	87	2.39	425	1.03	2.31	<0.0001
Total burden	2811	77.37	14927	36.22	2.13	<0.0001

CNS, central nervous system.

[a]Adverse event rates (events/100 patient months) in the first 12 months after implant for primary left ventricular assist device with implant device strategy bridge to transplant, bridge to candidacy, and destination therapy.

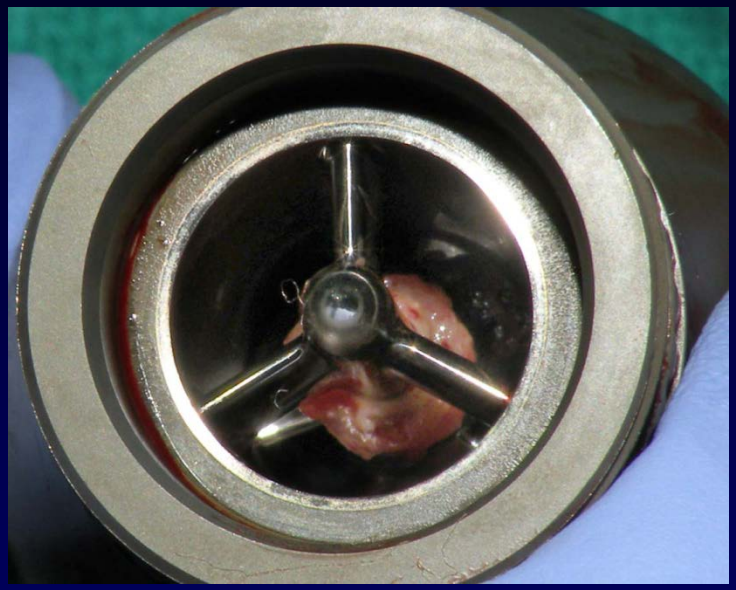
[b]With current reporting, identification of hypertension with continuous-flow pumps is unreliable.

Focus and attention with LVADs had been on risk of thrombosis and thromboembolic events early, over the last ten years it became clear that bleeding events became most relevant.

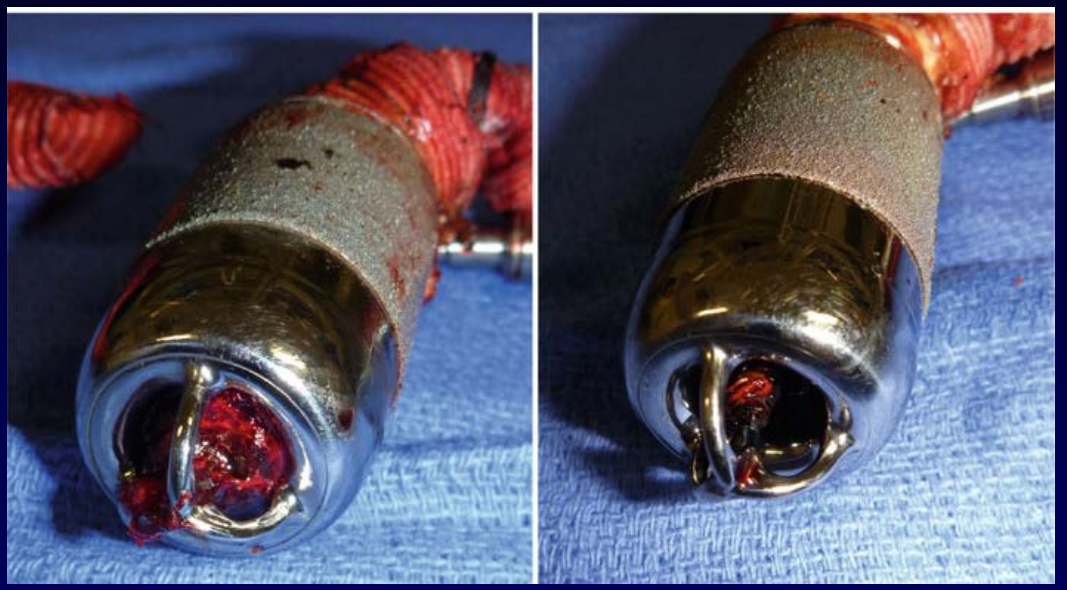
Although bleeding and infection are more common than thrombosis, the consequences of thrombosis can be devastating. It requires surgical pump exchange and in some cases, results in death and end-organ infarction/cerebrovascular infarction (neurologic event).

LVAD Thrombosis

HeartMate II



Jarvik 2000



Confirmed plus suspected pump thrombosis: 12%
Starling, NEJM 2014; 370(1):33-40

15-20% pump malfunction rates, Loebe et al., ISHLT 2013

Saito et al., J Artif Organs (2013) 16:105–109

(11% for old pin-bearing, personal communication)
(4% for new cone-bearing, personal communication)

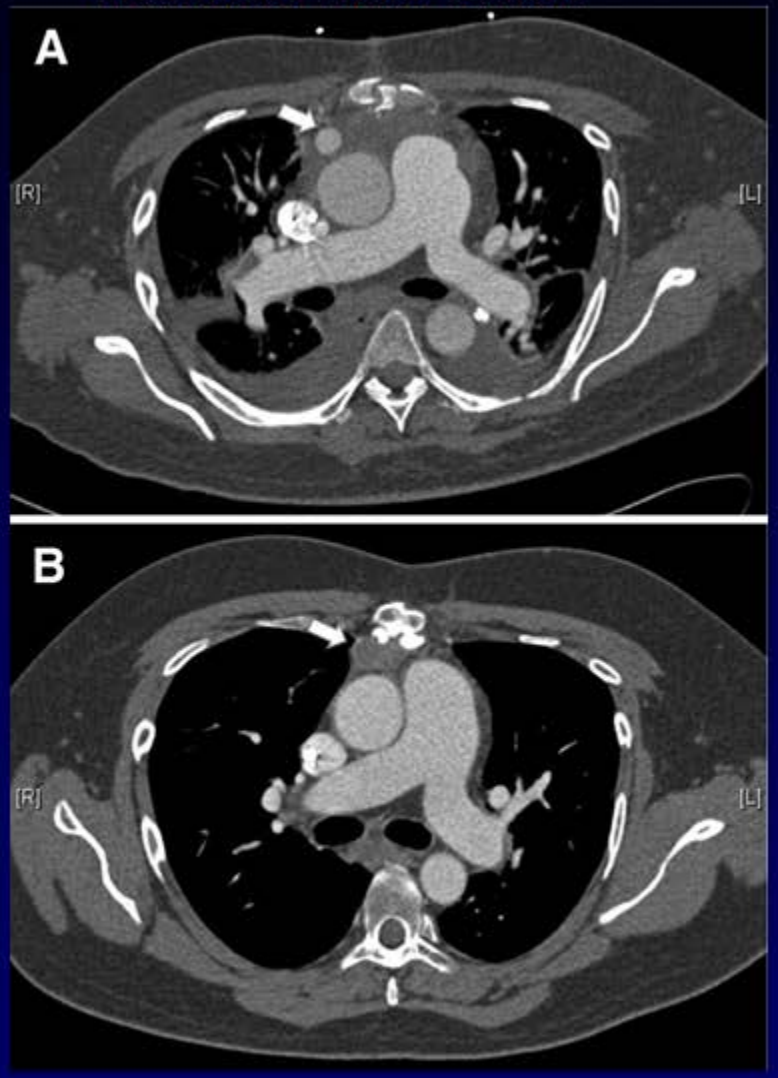
LVAD Thrombosis

HeartWare HVAD

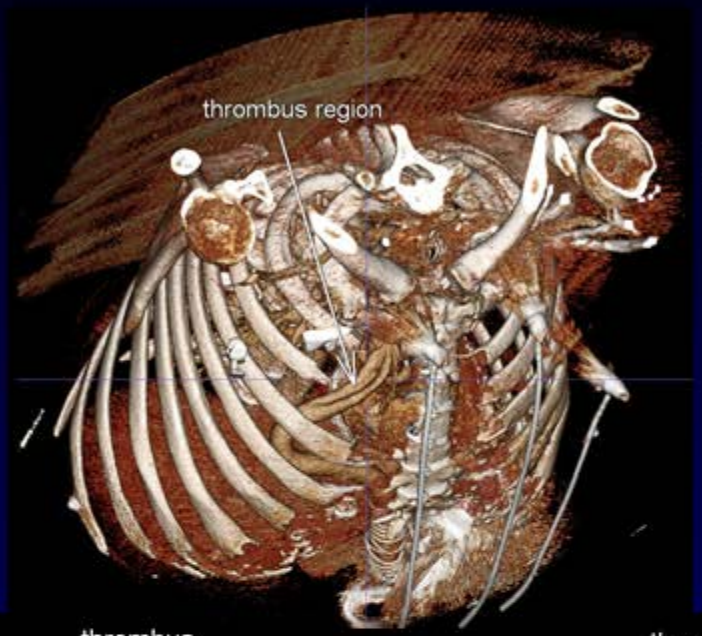
Events: 8.1% , Najjar, et al. JHLT 2014; 33:23-34

Outflow Graft Thrombosis

HeartWare HVAD Patient



Dimarakis et al., JTCVS2014;1-2



HeartMate II Patient

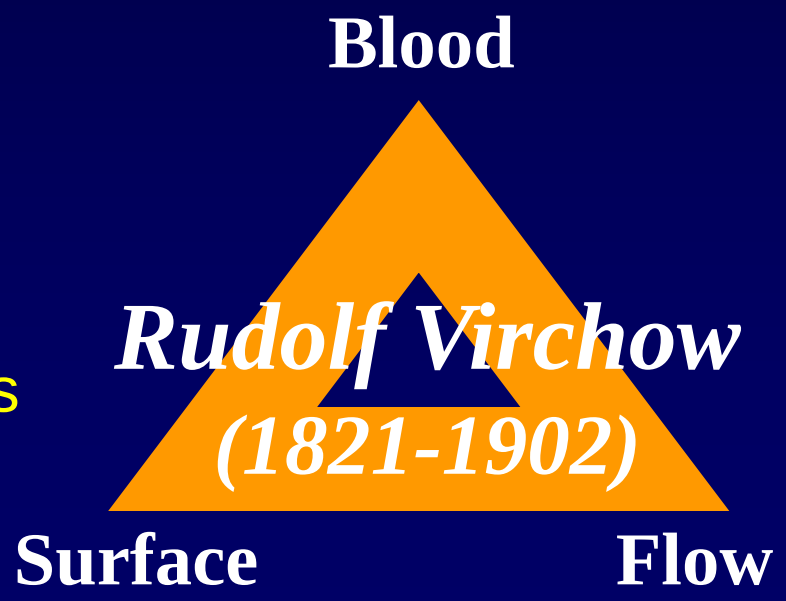
Thrombosis and Bleeding

A Vexing Problem in Long-term Use

Although significant progress have been made with use of VAD in patients, there is still a great deal of unknowns. The understanding of how these devices tilt the delicate intrinsic balance of bleeding and thrombosis is critical to guide therapy and to improve the long-term safety.

Contributing Factors:

- Non-physiological flow dynamics associated with device design and operation
- Non-biological materials
- Hemostatic properties and responses of patients to the above non-physiological conditions

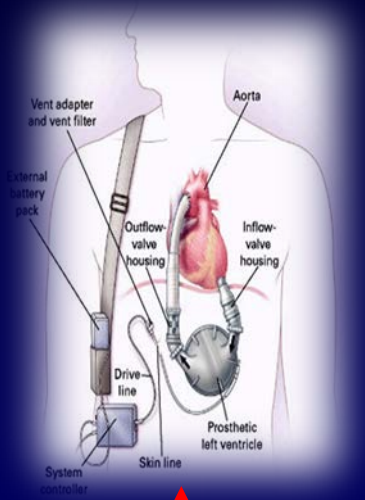


From Concepts to Clinical Use
Systems Engineering and Collaboration

Academia:
Basic Science
Bioengineering

Physicians:
Surgeons
Cardiologists

Patients

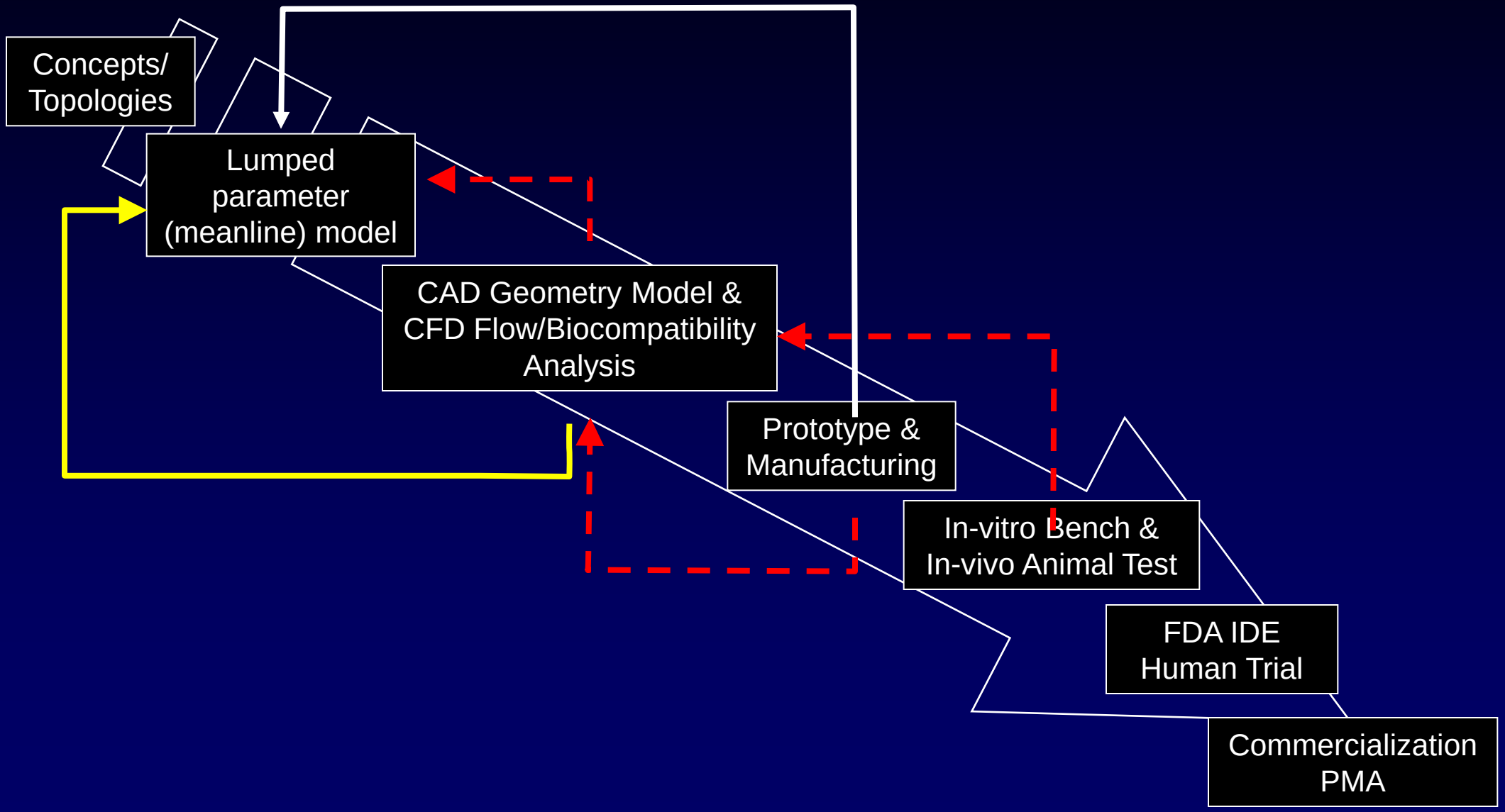


Industry:
Business
Manufacturing
Quality Control

Veterinary Medicine:
Pre-Clinical Evaluation

Government:
Regulation
Funding
Polcies

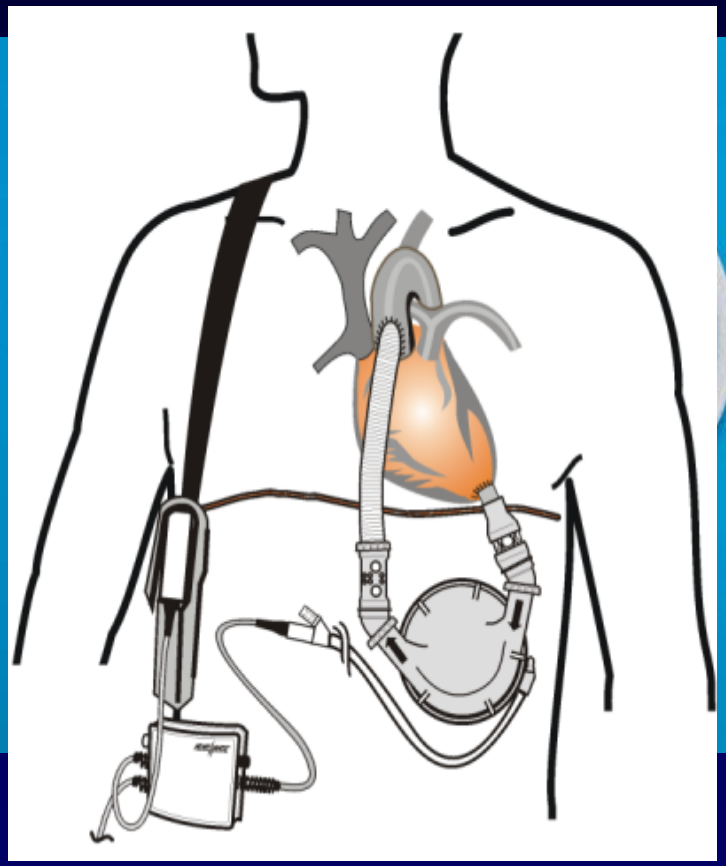
From Concepts to Clinical Use

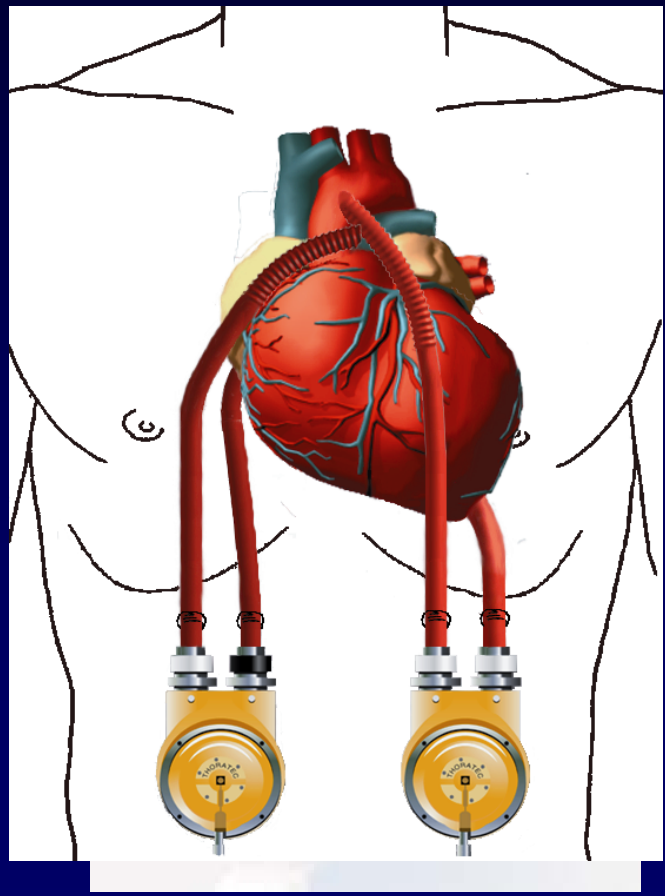


Topologies

Pulsatile VAD

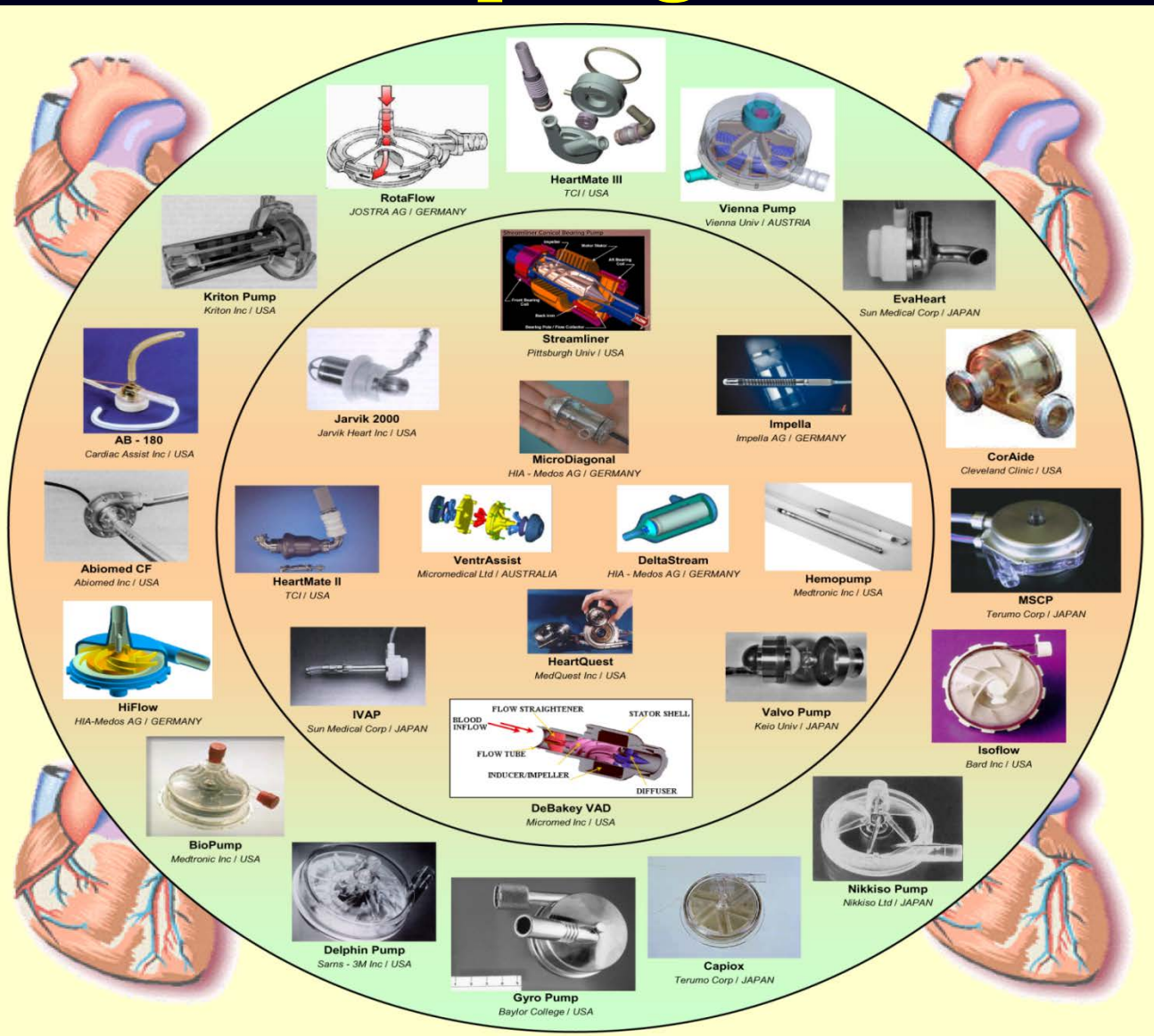
- Pneumatic vs. Electromechanical
- Internal vs. external





Topologies

Co
- Ax
- Int
- Be
- Fu



Integrated Design and Analysis

Traditional Approach – "Trial and Error"

CFD-Based Multidisciplinary Analysis and Optimization (MA&O) Framework

Initia … sting

CAD … ting

Geo … Size
G… ure

… ap,
etc.

Flo… and
Field Simulation | Model | Transport Model | Thrombosis Model

CFD Based Modeling of Functions and Performances

Fluid Dynamics

$$\rho\nabla\cdot\left(\vec{v}\vec{v}\right)=-\nabla p+\nabla\cdot\overline{\tau}+\rho\vec{g}+S$$

$$\nabla\cdot\vec{v}=0$$

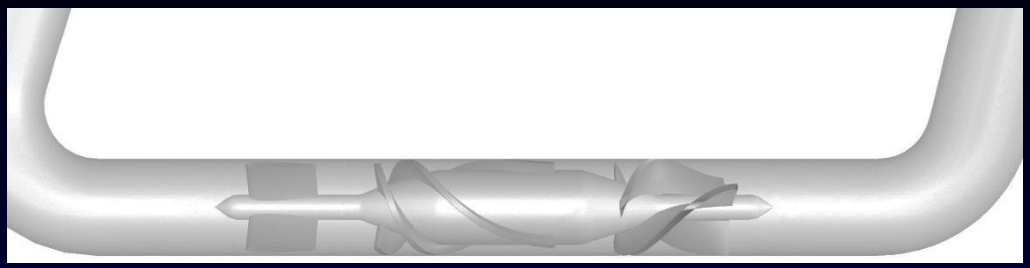
$$\tau=\left[\frac{1}{6}\sum\left(\tau_{ii}-\tau_{jj}\right)^2+\sum\tau_{ij}\tau_{ij}\right]^{\frac{1}{2}};\quad i,j,k=1,2,3;\ \ i\neq j\neq k$$

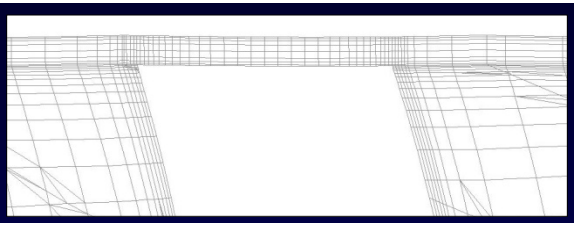
Hemolysis

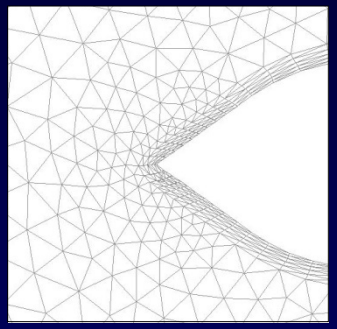
$$D_I=\frac{\Delta Hb}{Hb}\%=3.62\times10^{-5}t_{\exp}^{0.785}\tau^{2.416}$$

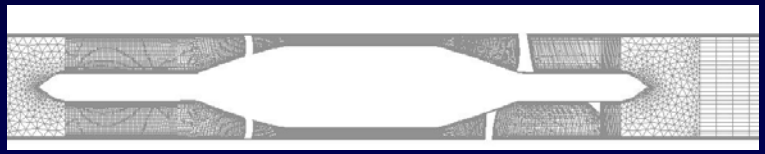
$$\frac{\partial c}{\partial t}+\left(\vec{u}\bullet\vec{\nabla}\right)c=\vec{\nabla}\bullet\left(D\nabla c\right)+S_I$$

Use of CFD in Development and Design Process

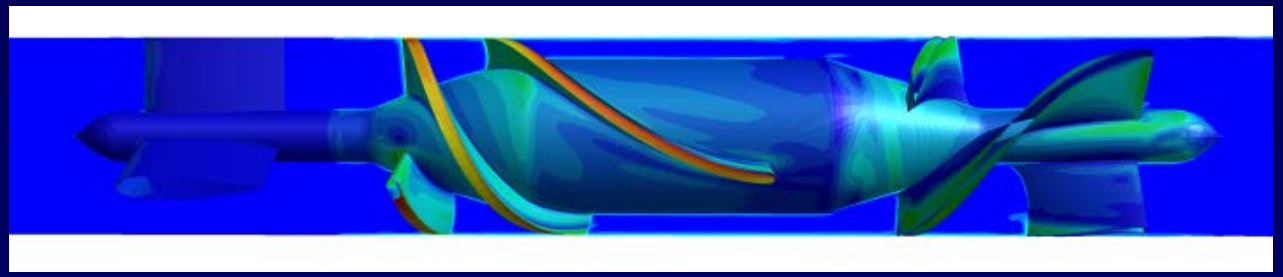


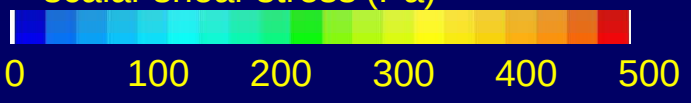


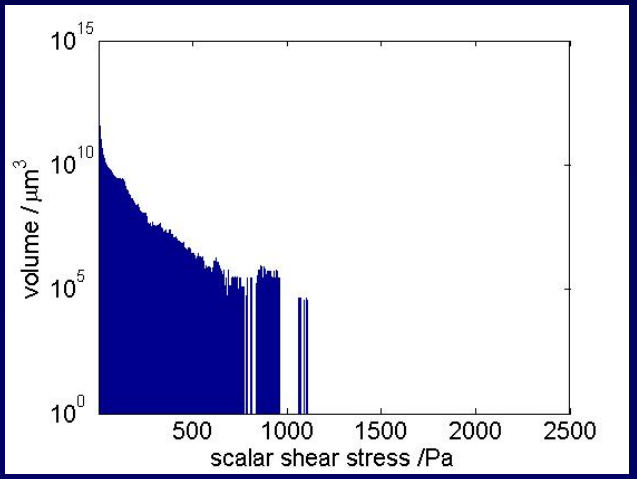




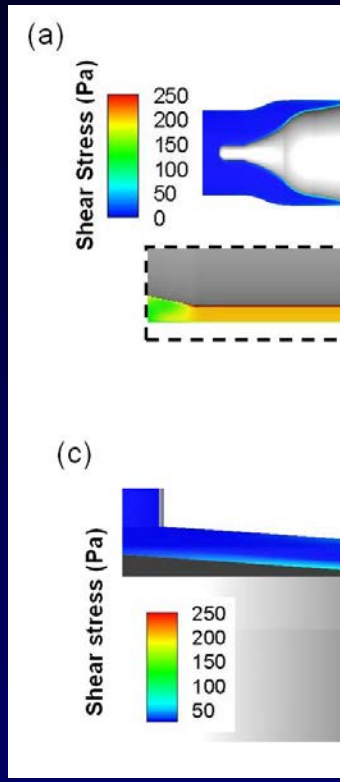
speed = 10k rpm, flow = 5 l/min,
pressure = 70 mmHg

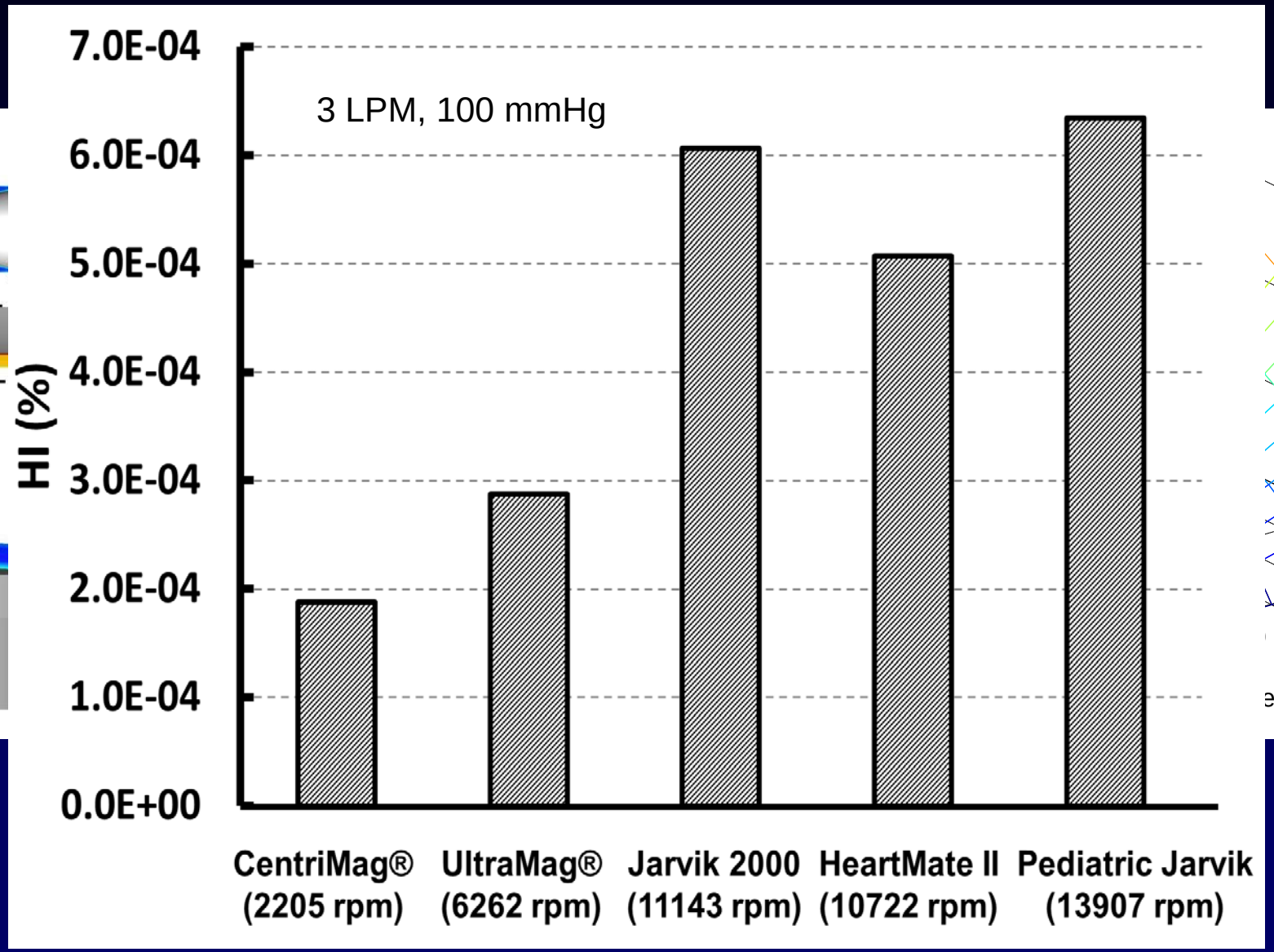


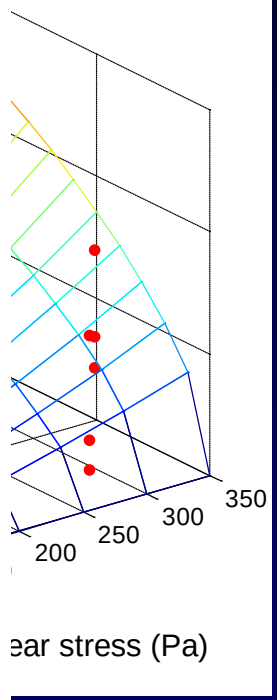




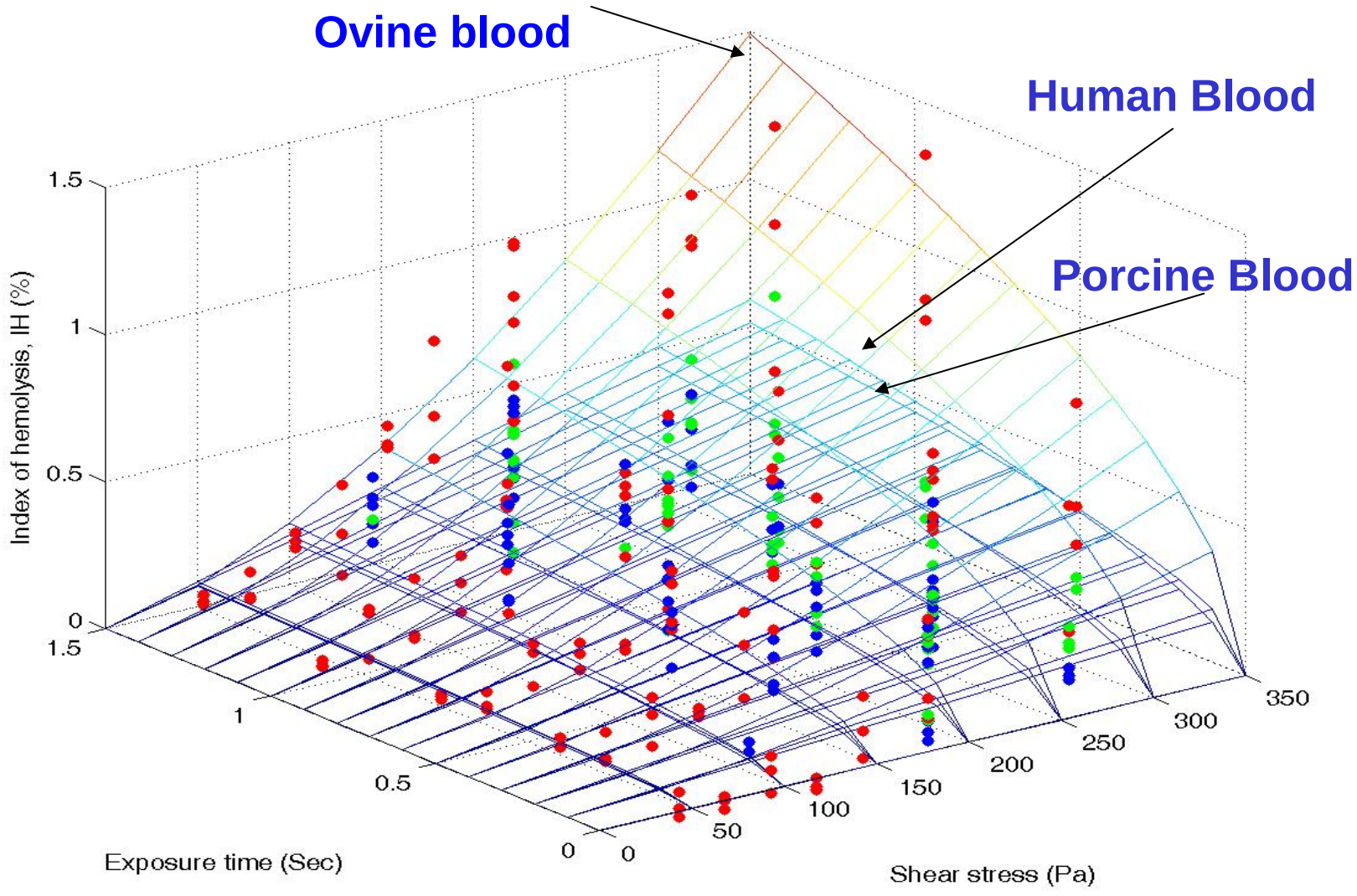
Shear-Induced Hemolysis (ovine blood)



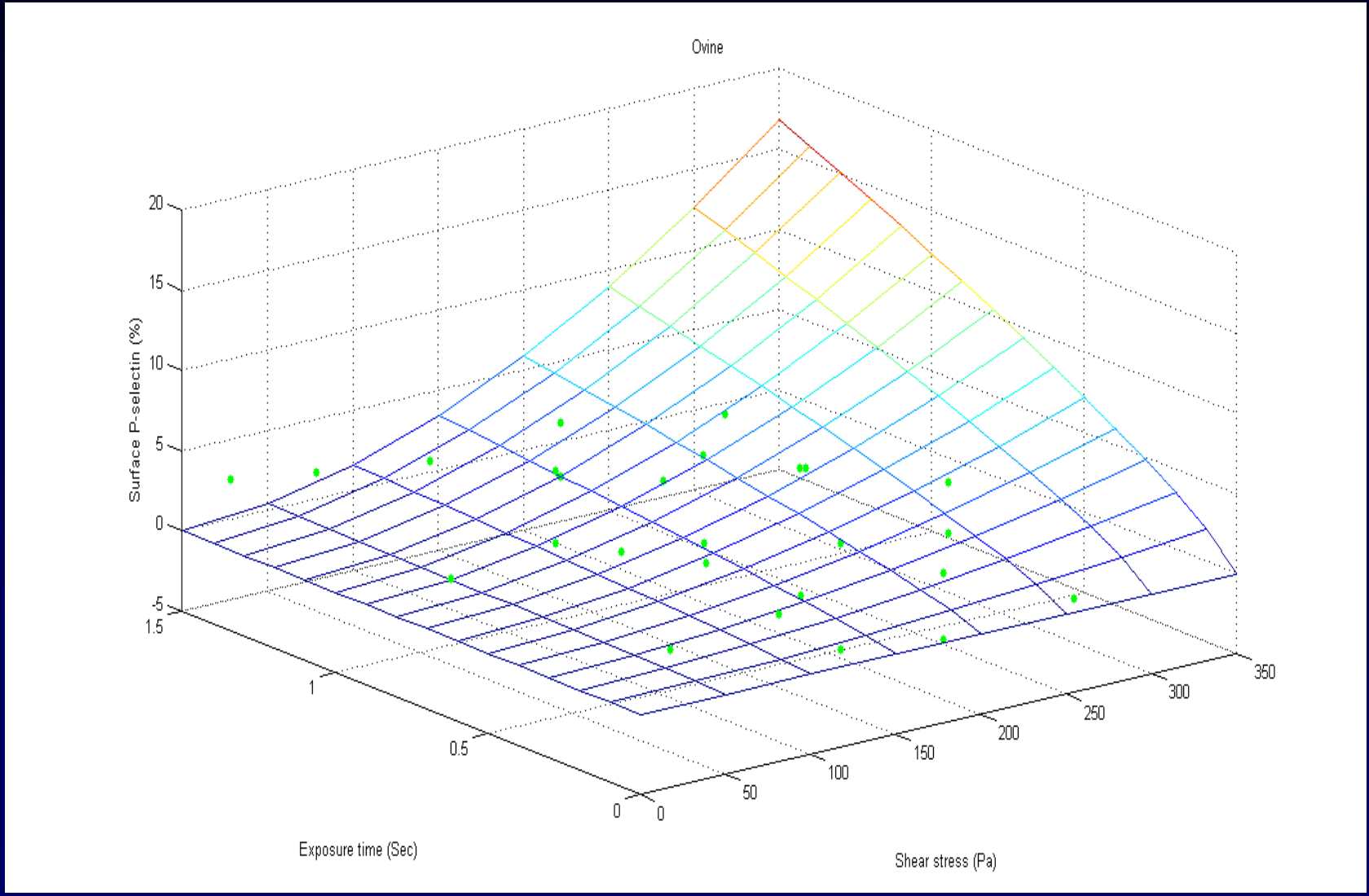




Shear-Induced Hemolysis
Species Difference



Shear-Induced Platelet Activation (Power-law Model)



Continuous Model of Platelet Activation in Devices

$$\frac{\partial c_i}{\partial t} + \left(\vec{u} \bullet \vec{\nabla}\right) c_i = \vec{\nabla} \bullet \left(D_i \nabla c_i\right) + s_i$$

Resting platelet: (C_{rp})

$$s_{rp} = -k_{pa} \cdot c_{rp} - c_{sd}^{\beta s} \cdot c_{rp}$$

Activated platelet: (C_{ap})

$$s_{ap} = +k_{pa} \cdot c_{rp} + c_{sd}^{\beta s} \cdot c_{rp}$$

Platelet released agonists: (C_{apr})

$$s_{apr} = +\lambda_j k_{pa} \cdot c_{rp} - k_{1,j} \cdot c_{apr}$$

Platelet synthesized agonists: (C_{aps})

$$s_{aps} = +s_{pj} \cdot c_{ap} - k_{1,j} \cdot c_{aps}$$

Prothrombin: (C_{pt})

$$s_{pt} = -\beta \cdot c_{pt} \left(\phi_{at} \cdot c_{ap} + \phi_{rt} \cdot c_{rp}\right)$$

Thrombin: (C_t)

$$s_t = -\Gamma \cdot c_t + c_{pt} \left(\phi_{at} \cdot c_{ap} + \phi_{rt} \cdot c_{rp}\right)$$

ATIII: (C_{at})

$$s_{at} = -\Gamma \cdot \beta \cdot c_t$$

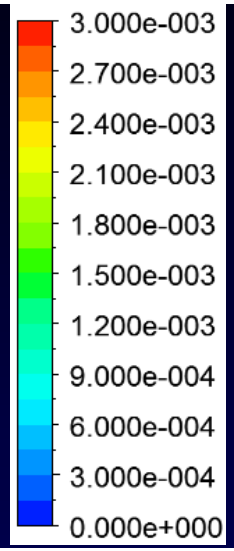
Shear Dose: (sd)

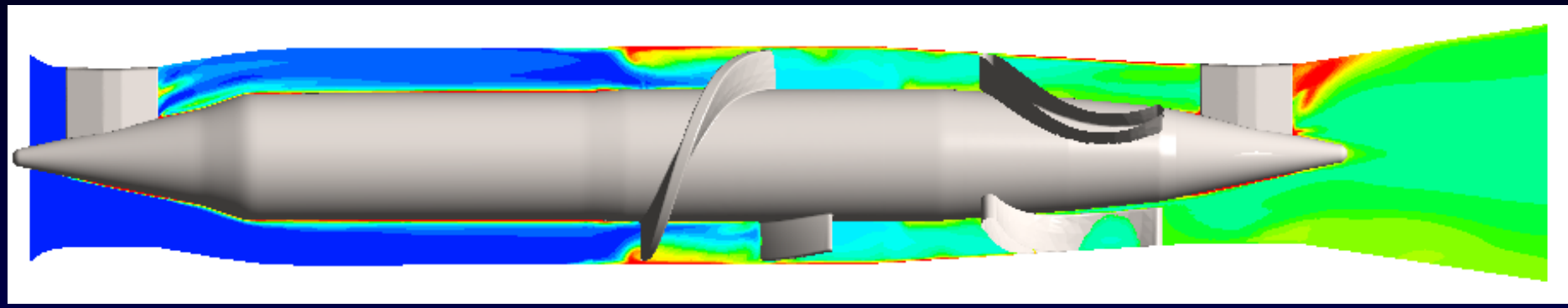
$$s_{sd} = sss^{\alpha s / \beta s} \cdot cons^{1/\beta s}$$

So far only ADP, prothrombin, thrombin, TxA2 and AT are considered in the model.

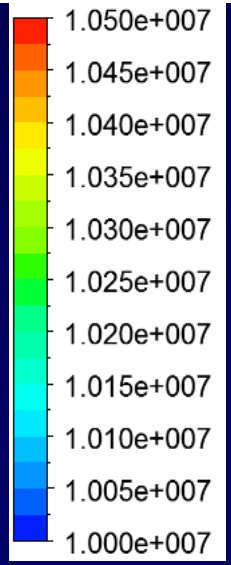
Platelet Activation in Jarvik 2000 Infant Pump

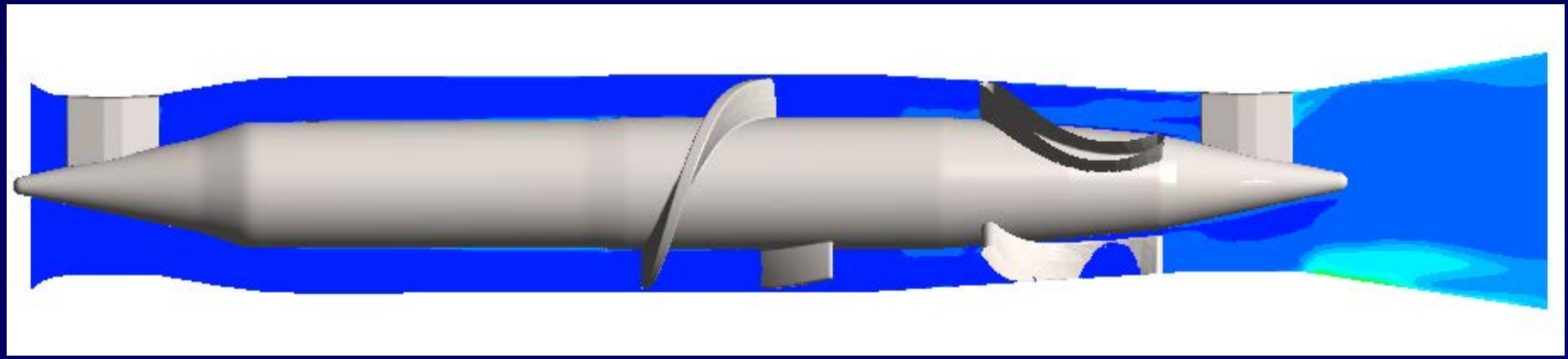
Shear dose/probability of activation:



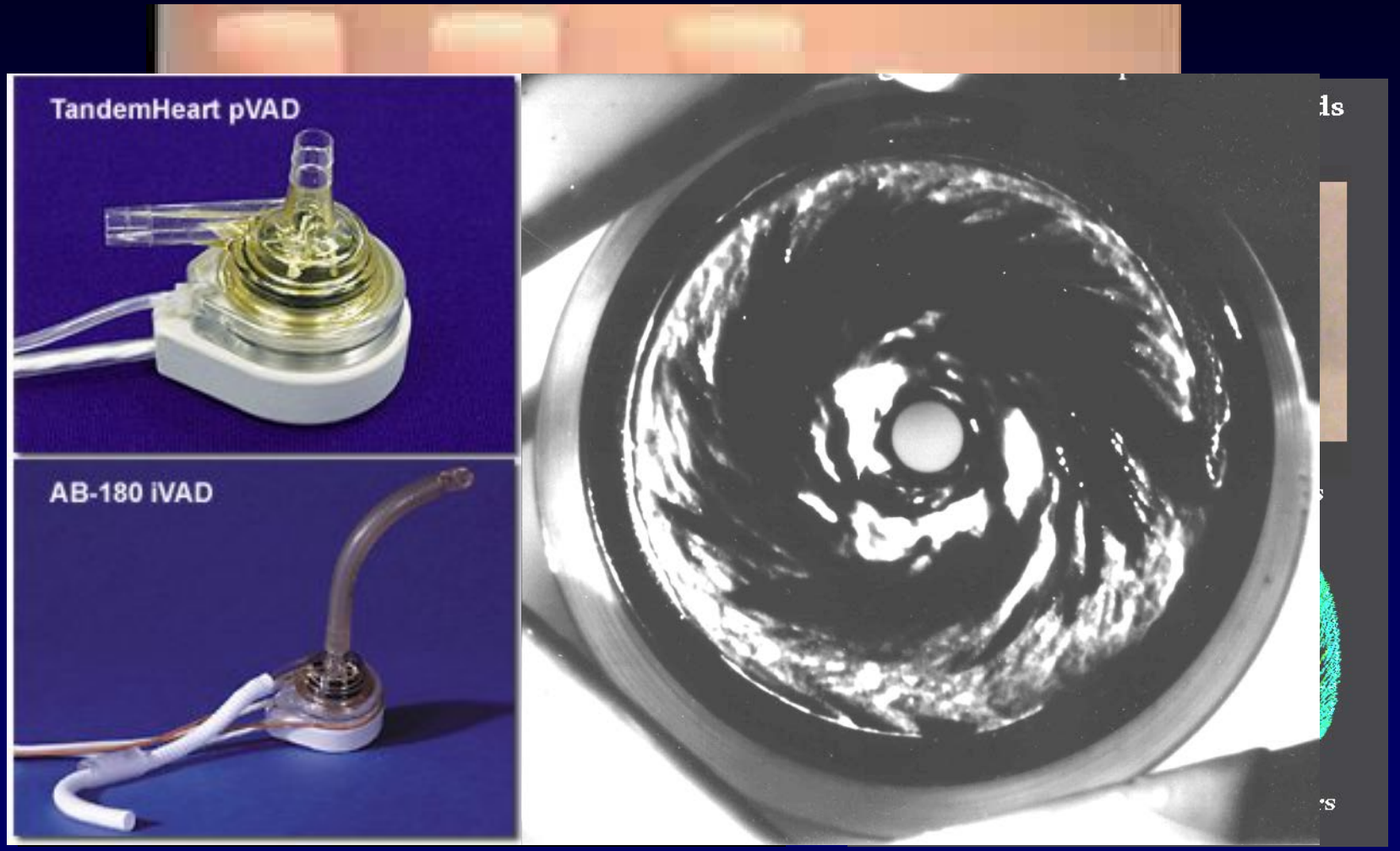


Number density of activated platelet





Surface Flow Visualization with Oil Dots



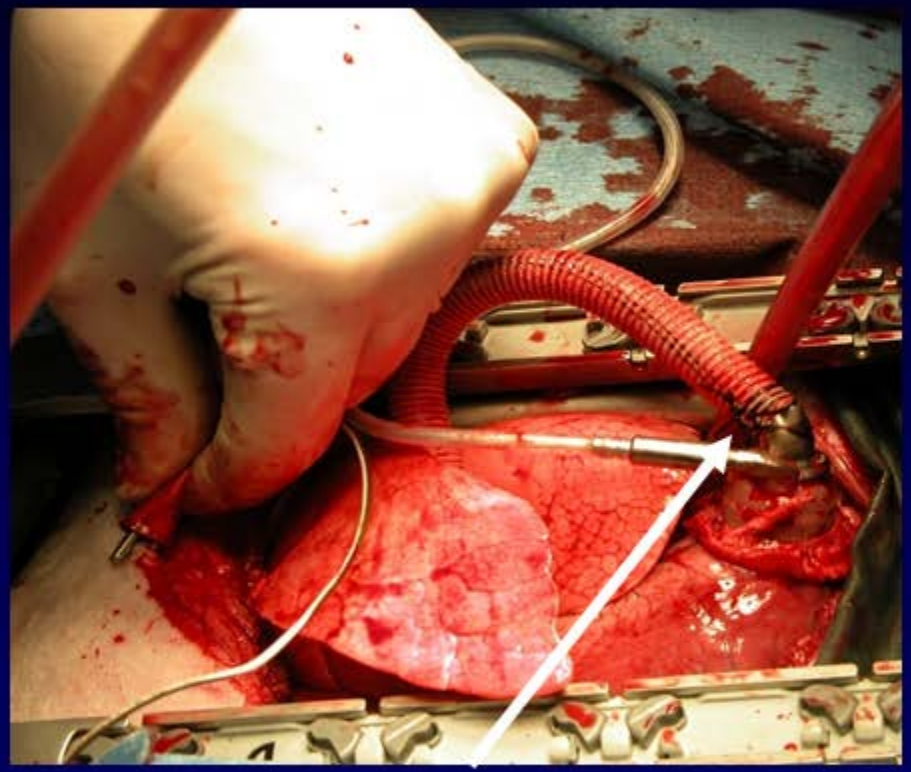
In-Vitro Testing of Function and Biocompatibility

RBC damage
- Plasma free hemoglobin

Platelet Activation Markers
- Platelet counts
- CD62p Expression
- Soluble CD62p concentration
- Platelet derived microparticles
- Platelet aggregates
- Platelet leukocyte aggregates

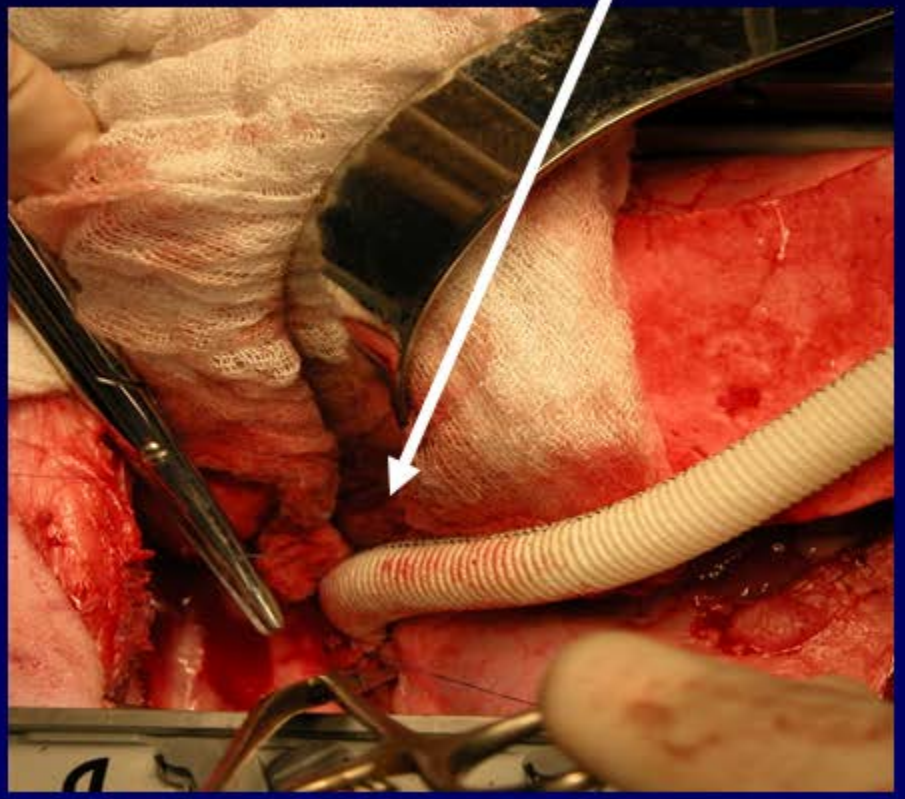
Thrombosis
- Platelet deposition
- Thrombosis formation

In-Vivo Evaluation in Animals



Intraventricular Apical Placement

Descending aorta (10 mm graft)



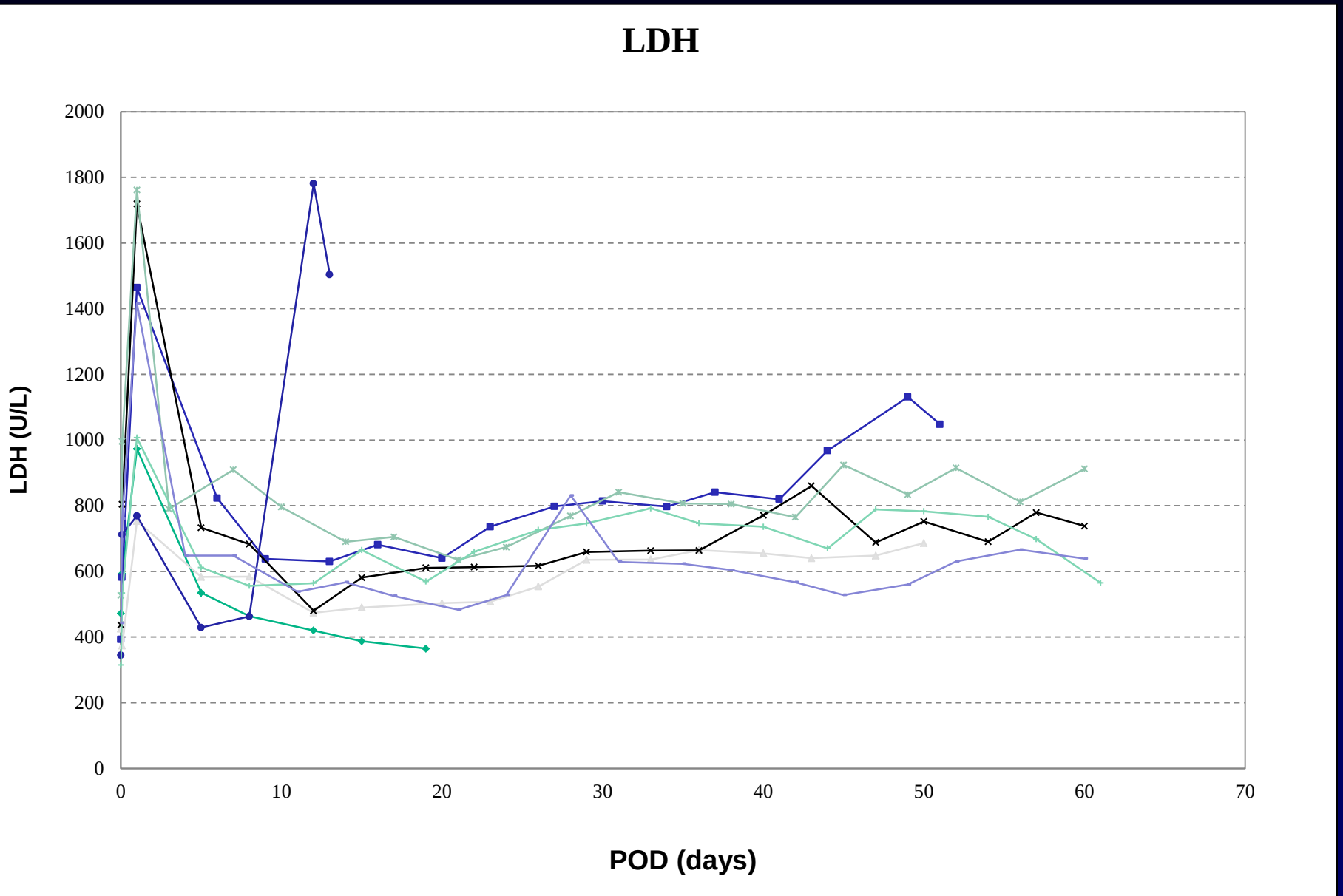
In-Vivo Evaluation in Animals

In-Vivo Evaluation - Methods

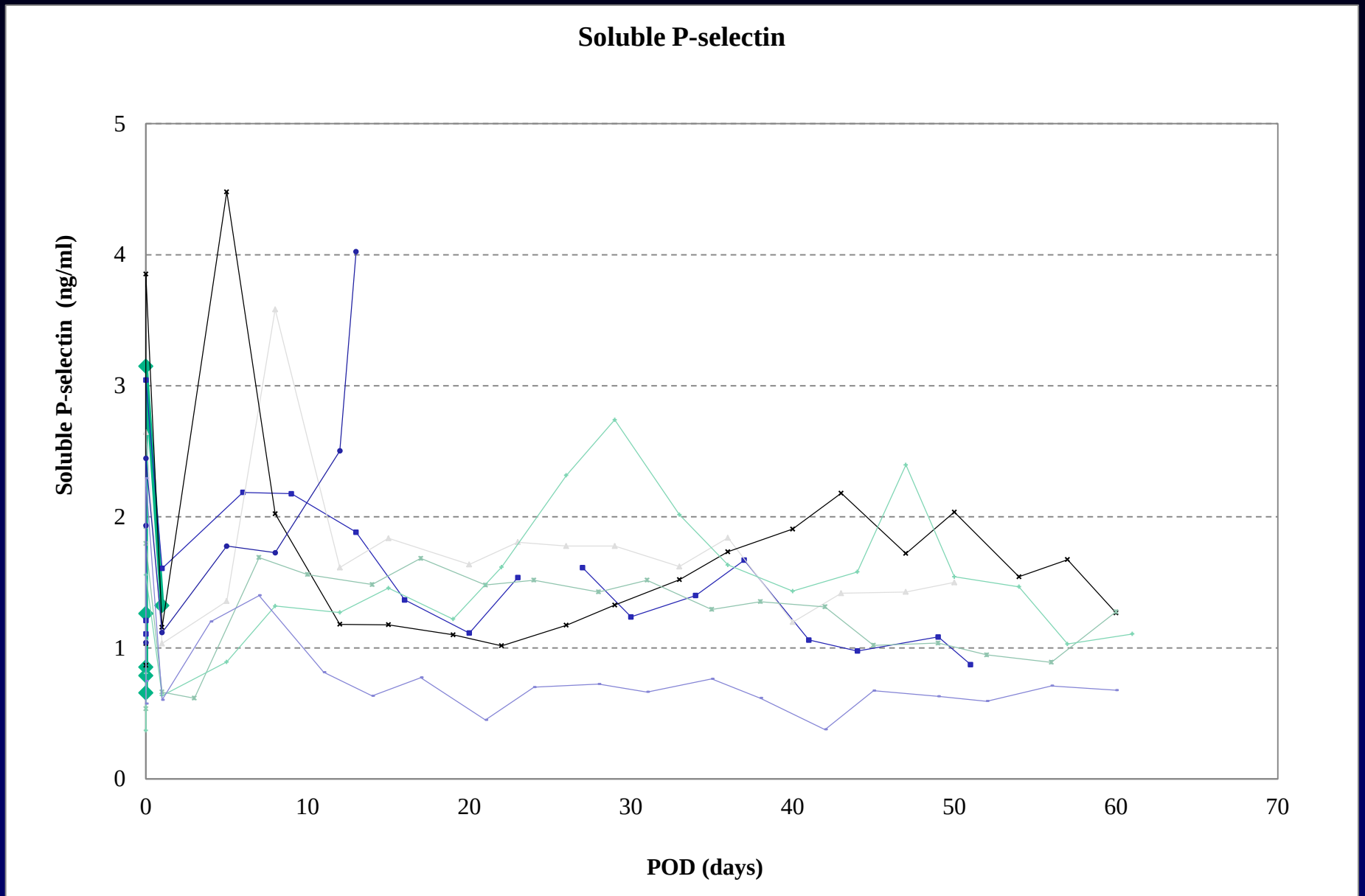
- **Hemodynamics**
  - Flows
    - Cardiac output (PA)
    - Device flow
  - Acute
  - Chronic
- **Device Operating Parameters**
  - Speed, Current, Power
- **Necropsy**
  - Gross
  - Histology

- **Biocompatibility/Biologic Response**
  - Hemolysis: pFH, LDH
  - Hematology: Hct, platelet counts
  - Infection: WBC/differential
  - Renal Function: creatinine
  - Liver Function, AST, ALT
  - Platelet Activation
    - Flow cytometry
    - ELISA
- **Schedule**
  - Baseline
  - Post-implantation
  - Twice a week after Implantation

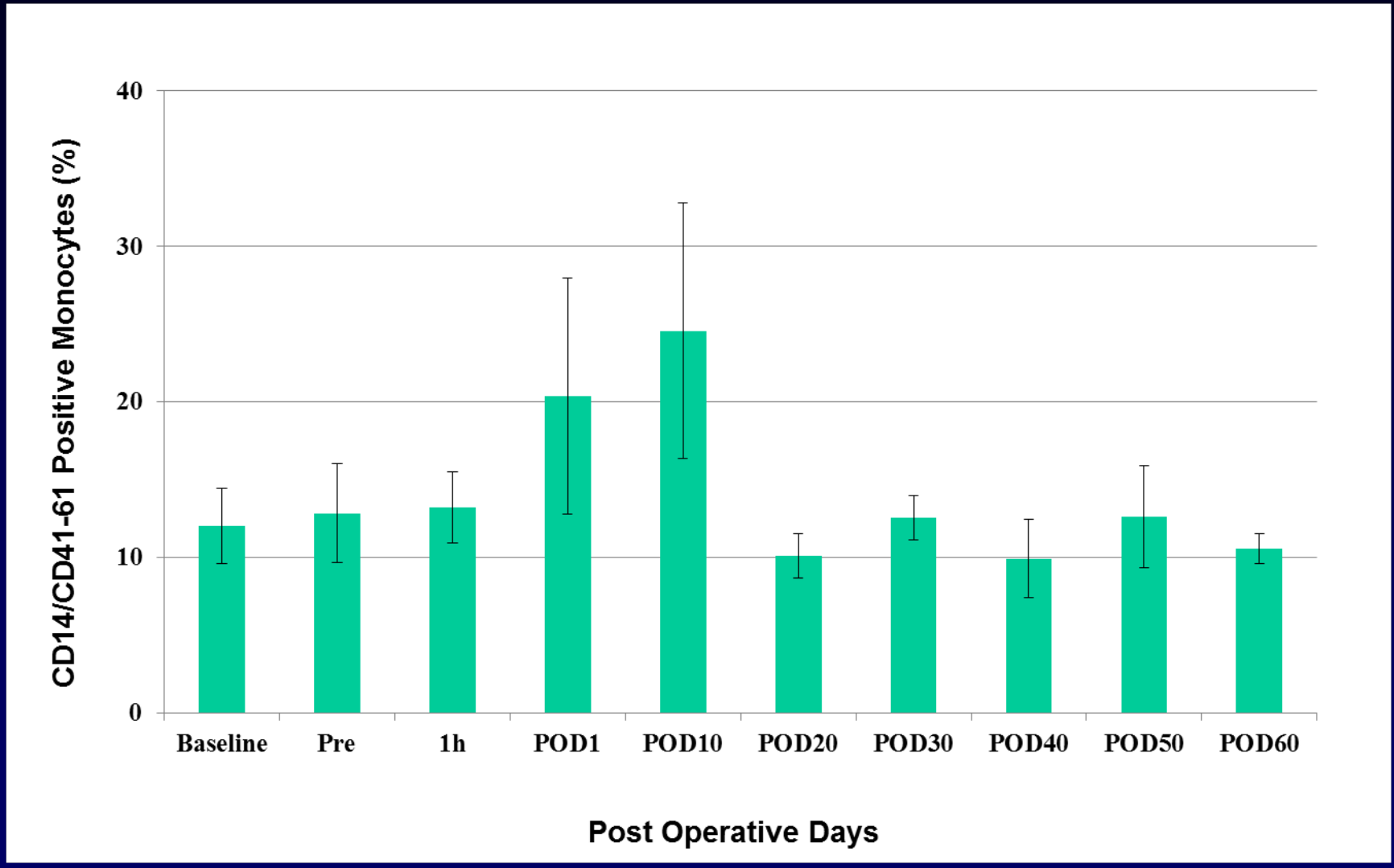
Hemolysis


LDH
LDH (U/L)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
10
20
30
40
50
60
70
POD (days)

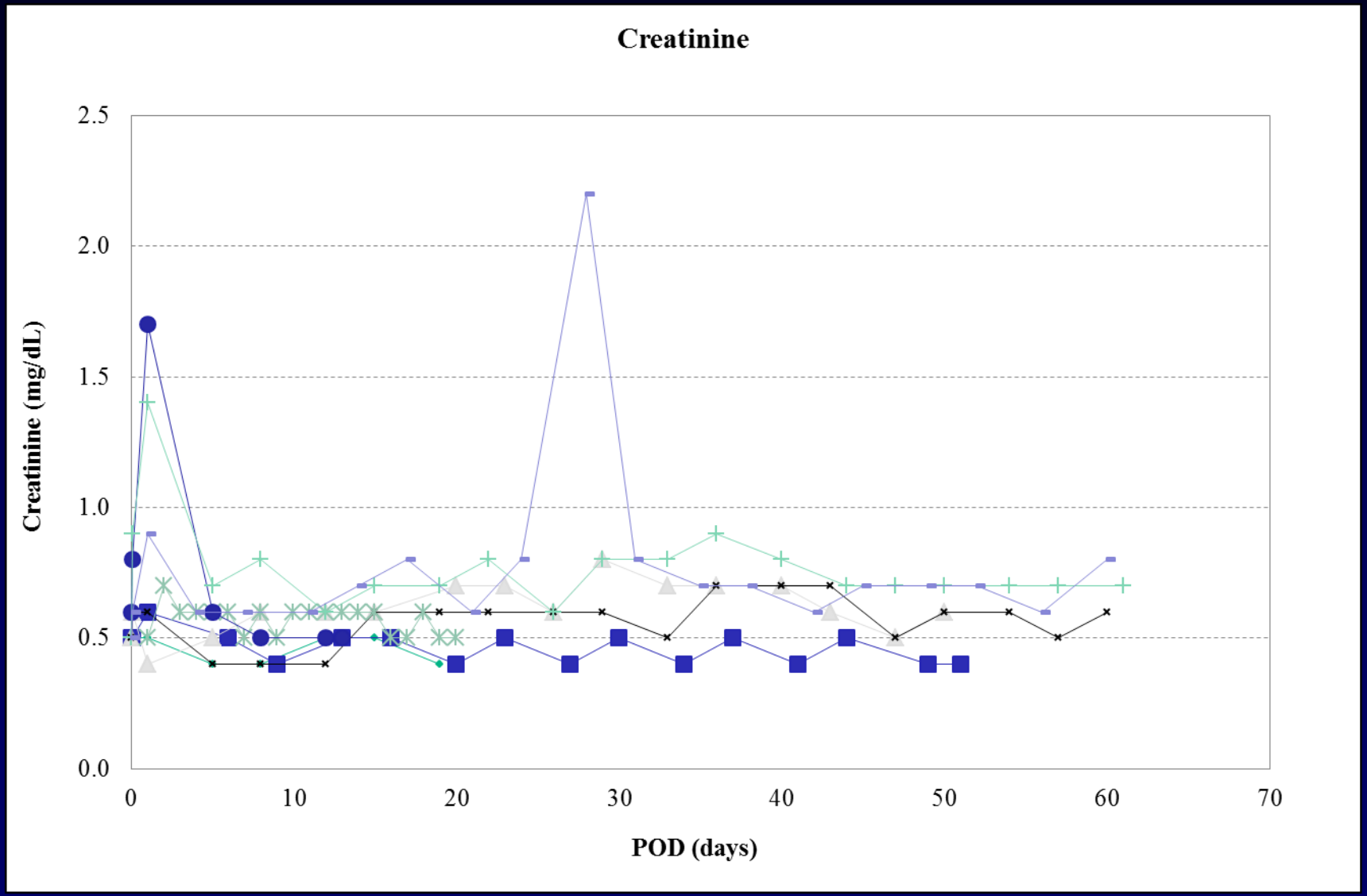
Platelet Activation Markers



Platelet/Monocyte Aggregates

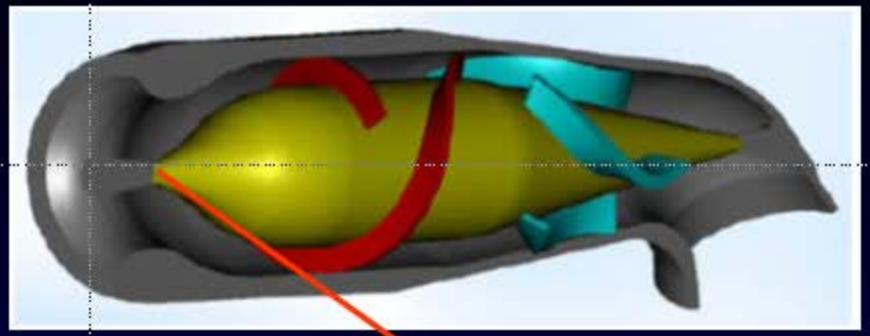


End-Organ Function Markers

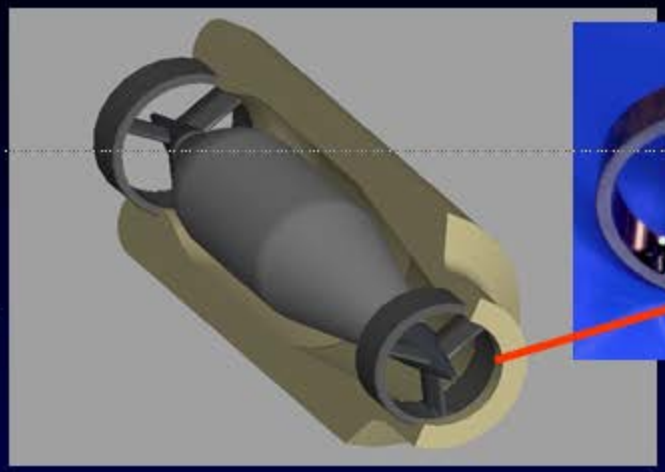


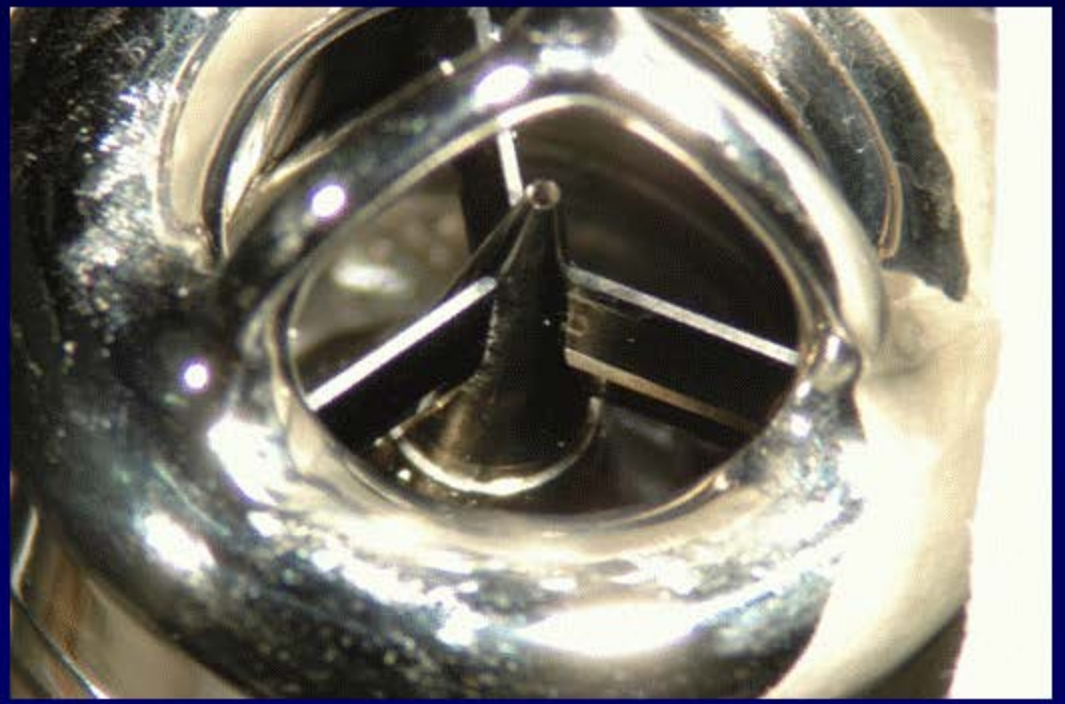
Necropsy

Pump Thrombosis



Explanted Pump after 60 Days





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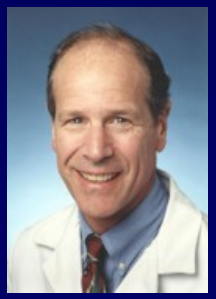
- NIH/NHLBI R01 HL118372
- NIH/NHLBI HHSN268201000014C

Artificial Organs Laboratory

- A multidisciplinary team of surgeons, biologists, and engineers
- Ongoing projects
  - Cardiac remodeling and novel therapies (VAD unloading, stem cells, molecular)
  - Artificial organs (pediatric VAD, artificial pump lung)
  - Medical device related blood damage



Thank You!